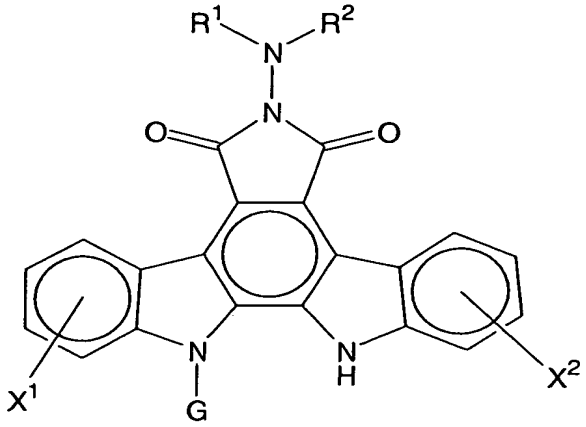
Replaced by IB 308, Substitue page 35-53

CLAIMS

1. A combined preparation for simultaneous, separate, or sequential administration in the treatment of cancer, comprising two separate preparations:

* a preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one compound of general formula I:



[I]

[wherein R^1 and R^2 each independently represent:

a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, aryl, aralkyl, or heterocyclic group (wherein the lower alkyl, the lower alkenyl, the lower alkynyl, the aryl, the aralkyl, and the heterocyclic group may each have one to five of the same or different substituents selected from the group consisting of carboxyl, carbamoyl, sulfo, amino, cyano, mono-lower alkylamino, di-lower alkylamino, hydroxyl, and a halogen atom);

or a group of formula -Y-R^3 {wherein Y represents carbonyl, thiocarbonyl, or sulfonyl, and R^3 represents a hydrogen atom, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, lower alkoxy, hydrazino, amino, arylamino, carbamoyl, or heterocyclic group (wherein the lower alkyl, the cycloalkyl, the cycloalkyl-lower alkyl, the aryl, the aralkyl, and the heterocyclic group may each have one to four of the same or different substituents selected from the group consisting of a halogen atom, optionally protected hydroxyl, amino, carboxyl, carbamoyl, cyano, and lower alkoxycarbonyl in which the amino and the carbamoyl may each be further mono- or di-substituted by lower alkyl

optionally substituted by a substituent or substituents selected from the group consisting of a halogen atom, hydroxyl, amino, carboxyl, carbamoyl, and lower alkoxycarbonyl)}; or

a group of formula $-(CH_2)_m-R^4$ {wherein R^4 is pyridyl, furyl, or thienyl (wherein the pyridyl, the furyl, and the thienyl may each have one or two substituents selected from the group consisting of hydroxyl, lower alkoxy, hydroxy-lower alkyl, and hydroxy-lower alkenyl), and m is an integer of 1 to 3},

R^1 and R^2 are combined together to represent lower alkylidene (wherein the lower alkylidene may have one to four of the same or different substituents selected from the group consisting of amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, carboxyl, and sulfo), or

R^1 and R^2, together with the nitrogen atom to which they bind, form heterocyclic group (wherein the heterocyclic group may have, on said ring, lower alkyl optionally substituted by a group or groups selected from the group consisting of amino, hydroxyl, carboxyl, and sulfo),

G represents a pentosyl or hexosyl; and

X^1 and X^2 each independently represent a hydrogen atom, a halogen atom, amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, lower alkoxy, aralkoxy, carboxyl, lower alkoxycarbonyl, or lower alkyl] or a pharmaceutically acceptable salt thereof; and

* a preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents or a pharmaceutically acceptable salt thereof

(wherein the antitumor alkylating agents are nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, or temozolomide,

the antitumor antimetabolites are methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil, tegafur, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, or fludarabine,

the antitumor antibiotics are actinomycin D, doxorubicin, daunorubicin, neocarzinostatin, bleomycin, peplomycin, mitomycin C, aclarubicin, pirarubicin, epirubicin, zinostatin stimalamer, or idarubicin,

the plant-derived antitumor agents are vincristine, vinblastine, vindeshine, etoposide, sobuzoxane, docetaxel, paclitaxel, or vinorelbine,

the antitumor platinum-complex compounds are cisplatin, carboplatin, nedaplatin, or oxaliplatin,

the antitumor campthotecin derivatives are irinotecan, topotecan, or campthotecin,

the antitumor tyrosine kinase inhibitors are Iressa or SU5416,

the monoclonal antibodies are IMC-C225, RhuMabVEGF, or Rituximab,

the interferons are interferon α, interferon α-2a, interferon α-2b, interferon β, interferon γ-1a, or interferon γ-n1,

the biological response modifiers are krestin, lentinan, sizofiran, picibanil, or ubenimex, and

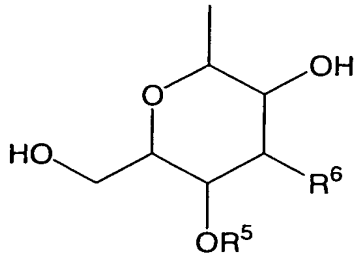
the other antitumor agents are mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, or tretinoin).

2. A combined preparation for simultaneous, separate, or sequential administration in the treatment of cancer, comprising two separate preparations:

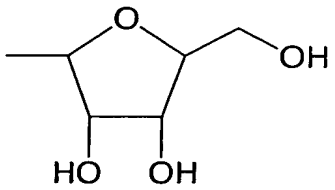
* a preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one compound of general formula I as defined in Claim 1 (wherein R^1, R^2, R^3, R^4, m, Y, G, X^1, and X^2 are the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof; and

* a preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one antitumor agent selected from the group consisting of: 5-fluorouracil; S-1; gemcitabine; doxorubicin and etoposide; docetaxel and paclitaxel; cisplatin, carboplatin, and oxaliplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; and IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof (wherein, if said preparation contains 5-fluorouracil, it may further contain leucovorin or may be combined with a separate leucovorin preparation).

3. A combined preparation as defined in Claim 2, wherein G is a group of formula:



or

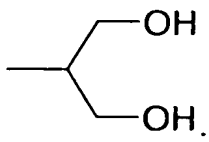


wherein R^5 represents a hydrogen atom or lower alkyl, and R^6 represents hydroxyl or amino.

4. A combined preparation as claimed in Claim 3, wherein X^1 and X^2 bind to the indolopyrrolocarbazole ring at the 1- or 2-position and at the 10- or 11-position, respectively, and each independently represent a halogen atom, hydroxyl, lower alkoxy, or aralkoxy.

5. A combined preparation as claimed in Claim 4, wherein G is β-D-glucopyranosyl, and X^1 and X^2 represent hydroxyl bonded to the indolopyrrolocarbazole ring at the 2-position and at the 10-position, respectively.

6. A combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents a group of formula:



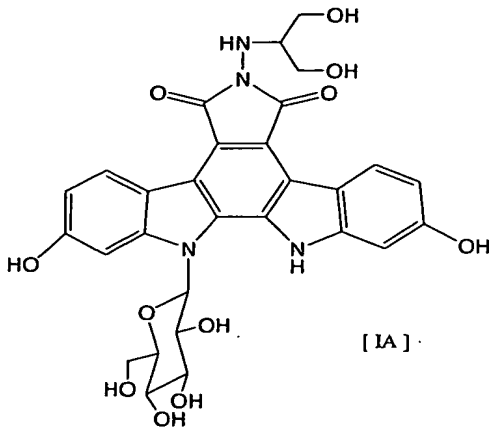
7. A combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2

represents $-CH_2-R^4$ in which R^4 represents 6-hydroxymethylpyridin-2-yl.

8. A combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents pyridin-4-yl.

9. A combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 5-hydroxymethylpyridin-4-yl.

10. A combined preparation as claimed in Claim 1 or 2, wherein the compound of general formula I as defined in Claim 1 is the compound of formula IA:



[IA]

11. A combined preparation as claimed in Claim 10, wherein one of or both of the two separate preparations according to Claim 1 is/are parenteral preparation(s).

12. A combined preparation as claimed in Claim 11, wherein one of or both of the two separate preparations according to Claim 1 is/are an injection or an infusion.

13. A combined preparation as claimed in Claim 12, which is further combined with at least one preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor

antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents (wherein a definition of each antitumor agent is the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof.

14. A method for cancer treatment, comprising administering to a cancer patient:

(a) a therapeutically effective amount of at least one compound of general formula I as defined in Claim 1 (wherein R^1, R^2, R^3, R^4, m, Y, G, X^1, and X^2 are the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof; in combination with

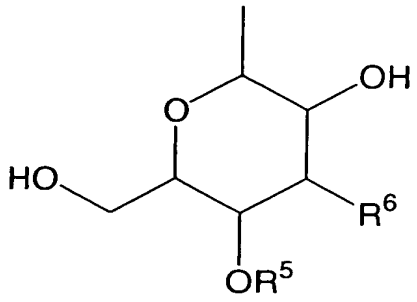
(b) a therapeutically effective amount of at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents (wherein a definition of each antitumor agent is the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof.

15. A method for cancer treatment, comprising administering to a cancer patient:

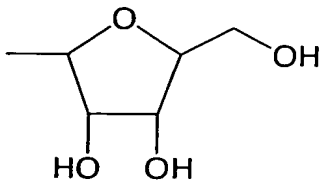
(a) a therapeutically effective amount of at least one compound of general formula I defined in Claim 1 (wherein R^1, R^2, R^3, R^4, m, Y, G, X^1, and X^2 are the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof; in combination with

(b) a therapeutically effective amount of at least one antitumor agent selected from the group consisting of: 5-fluorouracil; S-1; gemcitabine; doxorubicin and etoposide; docetaxel and paclitaxel; cisplatin, carboplatin, and oxaliplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; and IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof (wherein, if the compound of general formula I as defined in Claim 1 is combined with 5-fluorouracil, leucovorin may be further combined).

16. A method as claimed in Claim 15, wherein G is a group of formula:



or

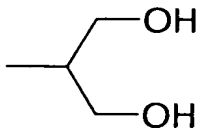


wherein R^5 represents a hydrogen atom or lower alkyl, and R^6 represents hydroxyl or amino.

17. A method as claimed in Claim 16, wherein X^1 and X^2 bind to the indolopyrrolocarbazole ring at the 1- or 2-position and at the 10- or 11-position, respectively, and each independently represent a halogen atom, hydroxyl, lower alkoxy, or aralkoxy.

18. A method as claimed in Claim 17, wherein G is β-D-glucopyranosyl, and X^1 and X^2 represent hydroxyl bonded to the indolopyrrolocarbazole ring at the 2-position and at the 10-position, respectively.

19. A method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents a group of formula:

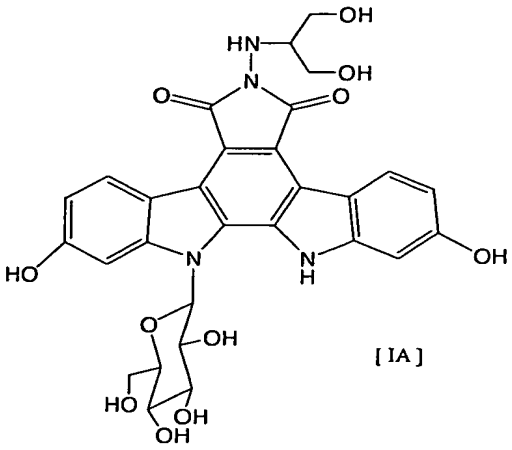


20. A method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 6-hydroxymethylpyridin-2-yl.

21. A method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents pyridin-4-yl.

22. A method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 5-hydroxymethylpyridin-4-yl.

23. A method as claimed in Claim 14 or 15, wherein the compound of general formula I as defined in Claim 1 is the compound of formula IA:



[IA]

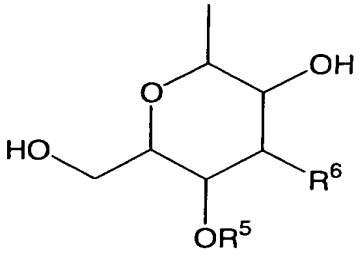
24. Use of at least one compound of general formula I as defined in Claim 1 (wherein R^1, R^2, R^3, R^4, m, Y, G, X^1, and X^2 are the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof; and

at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents (wherein a definition of each antitumor agent is the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof, for manufacturing a preparation for cancer treatment.

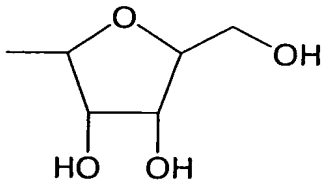
25. Use of at least one compound of general formula I as defined in Claim 1 (wherein R^1, R^2, R^3, R^4, m, Y, G, X^1, and X^2 are the same as defined in Claim 1) or a pharmaceutically acceptable salt thereof; and

at least one antitumor agent selected from the group consisting of 5-fluorouracil; S-1; gemcitabine; doxorubicin and etoposide; docetaxel and paclitaxel; cisplatin, carboplatin, and oxaliplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof, for manufacturing a preparation for cancer treatment.

26. Use as claimed in Claim 25, wherein G is a group of formula:



or

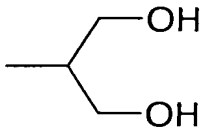


wherein R^5 represents a hydrogen atom or lower alkyl, and R^6 represents hydroxyl or amino.

27. Use as claimed in Claim 26, wherein X^1 and X^2 bind to the indolopyrrolocarbazole ring at the 1- or 2-position and at the 10- or 11-position, respectively, and each independently represent a halogen atom, hydroxyl, lower alkoxy, or aralkoxy.

28. Use as claimed in Claim 27, wherein G is β-D-glucopyranosyl, and X^1 and X^2 represent hydroxyl bonded to the indolopyrrolocarbazole ring at the 2-position and at the 10-position, respectively.

29. Use as claimed in Claim 28, wherein R^1 represents a hydrogen atom, and R^2 represents a group of formula:

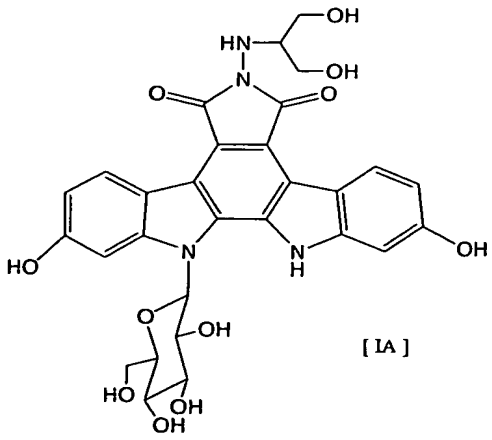


30. Use as claimed in Claim 28, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 6-hydroxymethylpyridin-2-yl.

31. Use as claimed in Claim 28, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents pyridin-4-yl.

32. Use as claimed in Claim 28, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 5-hydroxymethylpyridin-4-yl.

33. Use as claimed in Claim 24 or 25, wherein the compound of general formula I as defined in Claim 1 is the compound of formula IA:



[IA]

34. A pharmaceutical composition comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one compound of general formula I as defined above (wherein R^1, R^2, R^3,

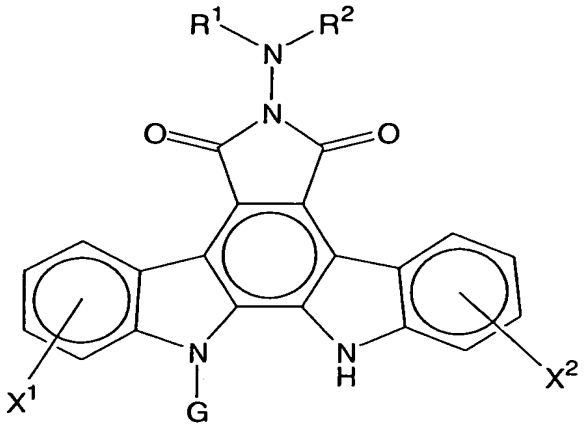
R^4, m, Y, G, X^1, and X^2 are the same as defined above) or a pharmaceutically acceptable salt thereof; and at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, biological response modifiers, and other antitumor agents (wherein a definition of each antitumor agent is the same as defined above) or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one compound of general formula I as defined above (wherein R^1, R^2, R^3, R^4, m, Y, G, X^1, and X^2 are the same as defined above) or a pharmaceutically acceptable salt thereof; and at least one antitumor agent selected from the group consisting of 5-fluorouracil; S-1; gemcitabine hydrochloride; doxorubicin hydrochloride and etoposide; docetaxel hydrate and paclitaxel; cisplatin, carboplatin, and oxaloplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof (wherein, if said composition contains the compound of general formula I and 5-fluorouracil, it may further contain leucovorin).

ABSTRACT

This invention relates to a combined preparation for simultaneous, separate, or sequential administration in the treatment of cancer, comprising two separate preparations:

* a preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one compound of general formula I:



[I]

wherein

R^1 and R^2 each independently represent a hydrogen atom, lower alkyl, or the like, and G represents pentosyl or the like, X^1 and X^2 each independently represent a hydrogen atom, a halogen atom, or the like or a pharmaceutically acceptable salt thereof; and

* a preparation, in combination with a pharmaceutically acceptable carrier or diluent, such as antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, or plant-derived antitumor agents (a preparation comprising at least one compound of general formula I or a pharmaceutically acceptable salt thereof may be combined with two or more other antitumor agents), and a method for cancer treatment comprising the administration of these preparations in combination.